REMARKS

Claims 1-51 are pending. Claims 1-3 and 5-7 are amended. No new matter has been added. Reconsideration is respectfully requested.

In the Office Action dated January 14, 2003, it is stated that the drawings are objected to because of the informalities as indicated by Draftsperson on PTO form 948. According to the Notice of Draftsperson's Patent Drawing Review issued to the present application on January 7, 2003, Fig. 19 does not have sufficient margin on the left (2.5cm), defined to A4 size.

The Applicants respectfully submit an amended Fig. 19 with proper margins. No new matter has been added to the drawings.

In the Office Action, it is stated:

> Claims 1-7, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Further, it is stated:

> The specification discloses three knockout mice, MyD88-/-, TLR2-/-, TLR4-/-, that are unresponsive to bacterial cell components. However, no other animal models unresponsive to bacterial cell components are disclosed.

and

> With limited information disclosed in the specification, an artisan would have not been able to predict whether mutation or deletion of the same genes in other non-human animal would result in the same phenotype compared to the disclosed knockout mice or mice harboring mutation in TLR4 gene.

And it is concluded that:

> the specification does not describe the invention in such a way to convey one skilled in the art the inventors had possession of the claimed invention at the time the application was filed.

Citing references, the Examiner attempted to establish the following:

(1) homologous recombination is required for gene targeting methods such as employed in the present invention,

(2) embryonic stem (ES) cell must be available to carry our the method,

(3) the only species in which the ES cell is available is the mouse (Bradley et al. bio/technology, vol.10, 534-539, 1992)

(4) There are no reports of any cell lines which contribute to the germ line in any species other than the mouse (Campbell and Wilmut, 1997, p.65).

(5) Chin animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated.(Mullins et al. 1996, Clin. Invest. Vol. 97, no.7, 1557-1560)

In view of the points mentioned above, the Examiner concluded that it would have been impossible to produce knockout animals using species other than mouse at the time of application.

Applicants agree with points (1) and (2), but disagree with (3), (4) and (5), as explained below.

<u>(3) the only species in which the ES cell is available is the mouse (Bradley et al. bio/technology, vol.10, 534-539, 1992)</u>

Citing Bradley et al. (bio/technology, vol.10, 534-539, 1992) in the Office Action, the Examiner states that the only species in which the ES cell is available is the mouse (p.537-538).

However, as the Examiner points out, there is a description in Bradley et al. bio/technology, vol.10, 534-539, 1992, noting:

> "A number of reports have claimed the isolation of ES cells from farm animals such as pigs and sheep (J. Reprod. Fert. Suppl. 41:51-56, Theriogenology 34, 865-878). However, the description of these cell lines is yet to be supported by the demonstration that they can proliferate and differentiate in an embryo in vivo, contributing to somatic tissues or germ cells. ES cells offer the same potential advantages for the genetic engineering of large animals that have been realized in mice, namely the ability to preselect for a desired genetic modification and generate, delete, or directly modify endogenous genetic traits by using gene targeting protocols. In species in which conventional random integration transgenic are difficult to make the availability of the ES cell route offers the additional advantage of being able to preselect for a desired integration structure or site for a transgene. The existence of such cell lines would greatly enhance our ability to genetically modify farm animals for the purposes of species improvement or protein production." (Bradley et al. bio/technology, vol.10, 537-538, 1992)

Citing Bradley et al. bio/technology, vol.10, 537-538, 1992, the Examiner states that the description of these cell lines is yet to be supported by the demonstration that they can proliferate and differentiate in an embryo in vivo, contributing to somatic tissues or germ cells. However, Bradley et al. bio/technology, vol.10, 537-538, 1992 mentions J. Reprod. Fert. Suppl. 41:51-56 and Theriogenology 34, 865-878, wherein the isolation of ES cells from species other than mice. Therefore, the position that the only species in which the ES cell is available is the mouse is incorrect.

Further, in Campbell and Wilmut, 1997, cited below, it is stated that there are reports of ES-like cell lines in a number of species including pigs, sheep, cattle, and primates, and also of cultured cell populations which contribute to chimeras in rat, pig and hamster. In view of this

statement, the position that the only species in which the ES cell is available is the mouse is not correct.

As stated above, a number of reports disclosing production of animal models of species other than the mouse have been made, and the art of producing animal models of species other than the mouse was within the knowledge of a person skilled in the art. Although mouse is often selected for the production of an animal model due to availability and economical efficiency, these factors are irrelevant to the patentability of the pending claims.

(4) There are no reports of any cell lines which contribute to the germ line in any species other than the mouse (Campbell and Wilmut, 1997, 65).

In the Office Action, citing Campbell and Wilmut, 1997, the Examiner states that there are no reports of any cell lines which contribute to the germ line in any species other than the mouse (pages 537-538).

However, Campbell and Wilmut, 1997, 65 state:

> "In species other than the mouse the isolation of ES cells has proven more difficult. There are reports of ES-like cell lines in a number of species including pigs (16) and sheep (17) cattle (18) and primates (19) and also cultured cell populations which contribute to chimeras in rat (20) pig (21) and hamster (22). However, as yet there are no reports of any cell lines which contribute to the germ line in any species other than the mouse." (Campbell and Wilmut, 1997, p.65)

It appears to be the Examiner's position that the above citation states that there are reports of ES-like cell lines and cultured cell populations in a number of species, but there are no reports of any cell lines which contribute to the germ line in any species other than the mouse.

However, as detailed above, a number of reports of producing animal models of species other than mouse have been made, and the art of producing animal models of species other than mouse was within the knowledge of a person skilled in the art. Although it is general that mouse is generally selected to produce animal models due to availability and economical efficiency, these factors are irrelevant to the patentability of the pending claims.

Further, the above citation states that ES cells are available in species other than the mouse. Therefore, it is respectfully suggested that the statement (3) is not supported by Campbell and Wilmut, 1997, either.

(e) Chin animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. (Mullins et al. 1996, Clin. Invest. Vol. 97, no.7, 1557-1560)

In the Office Action, citing Mullins et al. 1996, the Examiner states that there are reports of ES-like cells from various species but no report of cell lines that contribute to germline transmission in species other than the mouse.

> Mullins et al., 1996, states:
> "Despite the lack of germline transmission to date, major efforts continue to be directed towards the generation and use of ES cells from nonmurine species, using both traditional and new technologies, and the availability of such cells is likely to accelerate both the use of such species and the precision with which genetic changes can be introduced." (p.1559)

As evident from the citation, germ transmission is not a necessary requirement in producing model murines; rather major efforts have been made to generate and use ES cells from nonmurine species. Therefore, it is respectfully submitted that the statement (4) is not supported by Mullins et al. 1996.

As already mentioned, ES cells are available in species other than the mouse. A person skilled in the art would be able to carry out the claimed invention of the present application with the disclosures of the specification and the knowledge of a person skilled in the art without carrying out undue experimentation.

In the Office Action, claims 1-7, 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the Office Action, it is stated:

> In the present instance, claims 1-7, 10 and 11 recite the broad range or recitation "unresponsive to bacterial cell components," and the claim also recites "unresponsive to a lipoprotein/lipopeptide" which is the narrower statement of the range/limitation. It is unclear whether the animal is required to be unresponsive to other bacterial cell components besides lipoprotein/lipopeptide.

The Applicants used "unresponsive to a lipoprotein/lipopeptide, which is a bacterial cell component" to refer to "unresponsive to a lipoprotein/lipopeptide as a bacterial cell component" from the time of filing the present application, and do not intend to use the words to refer to bacterial cell components other than lipoprotein/lipopeptide. Claim 1 has been amended to remove indefiniteness, and believe that the rejection is overcome.

The applicants amend claims 3, 5, 6, 7, which use words in parallel to claim 1, to remove similar. No new matter has been added, as the content of the amended claims was disclosed in the "BEST MODE for Carrying out the Invention" of the originally filed specification.

In the Office Action, it is stated:

> Regarding claims 1-7, 10 and 11, the term "characterized" renders the claims indefinite because it is unclear what is the characteristics Applicants are referring to. In other words, is the animal unresponsive to the lipoprotein only or other bacterial cell components as well?

Regarding this, the Applicants have amended claim1 comprising the word "characterized" to remove the indefiniteness of the claim. Indefiniteness of dependent claims 2-7, 10 and 11 is also removed by this amendment.

Still further, it is stated:

> Regarding claim 2, the word "derived" renders the claim indefinite because the nature and number of derivative process is unknown. As such, the meters and bounds of the claims cannot be established.

Claim 2 has been amended to replace the word "derived" with "obtained". No new matter has been added. Withdrawal of the rejection is respectfully requested.

Still further, it is stated:

> Regarding claim 6, the word "lopoteichoic" renders the claim indefinite because its meaning is unknown. It appears that the word is mis-spelled. Appropriate correction is required.

Regarding this, the Applicants have amended claim 6 to correct the spelling of lipoteichoic. The specification discloses lipoteichoic acids in the "Best Mode for Carrying out the Invention". No new matter has been added.

In the Office Action, it is stated:

> Claims 1, 3-6, 10 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Takeuchi et al. (1999, Immunity, Vol. 11, pp.443-451).

Further, it is stated:

> A certified English translation of the foreign priority document would remove the availability of the reference under 35 U.S.C. 102(a) if all the claimed subject matter were disclosed in the foreign priority document.

In the Office Action, it is stated:

(1) Takeuchi et al. disclose that TLR4 deficient mice are unresponsive to LPS induced shock,

(2) Takeuchi et al. also disclose that TLR2 deficient mice are unresponsive to S. aureus peptidoglycan induced NO2 production, and

(3) Takeuchi et al. further discloses that TLR4 deficient mice are unresponsive to lipoteichoic acid isolated from S. aureus.

Following the Examiner's suggestion, the Applicants respectfully submit a copy of declared English translation of the priority documents; JP11-007365, JP11-228282, JP11-309238. (1) to (3) listed above are disclosed in the priority documents as follows:

(1): Example 5, pages 25 to 33 of JP11-228282,

(2) Example 5, pages 20 to 21 of JP11-309238, and

(3) Example 5-10, page 35 of JP11-228282

(1) to (3) are all disclosed in the priority documents. Therefore, the priority is effective to the disclosures listed in (1) to (3) above, and therefore the rejections of claims 1, 3-6, 10 and 11 under 35 U.S.C. 102(b) as being anticipated by Takeuchi et al. (1999, Immunity, Vol. 11, pp. 443-451) do not stand.

In the Office Action, it is stated:

Claims 1, 3-5, 10 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Vacheron et al. (1983, Infection and Immunity, Vol. 42, No. 3, pp.1049-1054).

Further, it is stated:

Vacheron et al. disclose that murine thymocytes collected from CH3/HeJ mice are not responsive to peptidoglycan stimulation (see page 1051, 2nd paragraph, lines 4-5). Vacheron et al. also disclose that CH3/HeJ mouse macrophases are unresponsive to bacterial endotoxinlipopolysaachride (see page 1052, 1st col. last line through 2nd col. first line). Therefore, Vacheron et al. disclose the instant claimed invention.

Claims 2 to 5, 10 in the present application depend on claim 1, claim 11 depends on claim 10. If the claims were rejected as being anticipated by Vacheron et al., as stated in the Office Action, Vacheron et al. should also disclose that "a model non-human animal being unresponsive to bacterial cell components , which is unresponsive to a lipoprotein/lipopeptide as a bacterial cell component," as claimed in claim 1. It is not stated in the Office Action that there are such disclosures in Vacheron et al., nor are there such disclosures in Vacheron et al. Claims 2-5, 10 depend on claim 1, and claim 11 depends on claim 10, further depending on claim 1. Therefore, it is evident that claims in the present application should not be rejected as anticipated even though Vacheron et al. discloses "murine thymocytes collected from CH3/HeJ mice are not responsive to peptidoglycan stimulation" or "CH3/HeJ mice macrophages are unresponsive to bacterial endotoxin lipopolysaachride.

For these reasons, Applicants respectfully submit that the disclosures in Vacheron et al. noted by the Examiner are not relevant to the novelty of the claims of the present inventions.

In 1980's, there are a number of experiments conducted to examine the components of bacteria, using CH3/HeJ mice. However, the fact that the data in the references of this period, including Vacheron et al. Infection and Immunity, Vol. 42, No. 3, pp. 1049-1054, 1983, showing that murine thymocytes collected from CH3/HeJ mice are not responsive to peptidoglycan stimulation are not correct, was known at the time of filing the present application. For example, Vacheron F, Guenounou M, Zinbi H, Nauciel C. (Release of a cytotoxic factor by macrophages stimulated with adjuvant-active peptidoglycans. J Natl Cancer Inst. 1986 Aug;77(2):549-53.) show that C3H/HeJ mice are responsive to peptidoglycan. Further, Takada H, Kawabata Y, Kawata S, Kusumoto S. (Structural characteristics of peptidoglycan fragments required to primemice for induction of anaphylactoid reactions by lipopolysaccharides. Infect Immun. 1996 Feb;64(2):657-9.) use C3H/HeJ mice in examining the responsiveness to peptidoglycan in order

to exclude the effects of endotoxin. In other words, C3H/HeJ mice show the same responsiveness to peptidoglycan as normal mice do.

Therefore, the pending claims will not be rejected under 35 U.S.C. 102(b) as being anticipated by Vacheron et al. A copy of the references cited above are enclosed for the Examiner's convenience.

Accordingly, favorable consideration of the pending claims is respectfully requested.

Should the resolution of any minor issues place the application in condition for allowance, the Examiner is kindly invited to call the undersigned at the designated telephone number.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (amended) A model non-human animal being unresponsive to bacterial cell components, which is [characterized in being] unresponsive to a lipoprotein/lipopeptide as [which is] a bacterial cell component.

2. (amended) The model non-human animal being unresponsive to bacterial cell components according to claim 1, wherein a lipoprotein/lipopeptide is a macrophage-activating lipopeptide obtained [derived] from bacteria which belong to Mycoplasma.

3. (twice amended) The model non-human animal being unresponsive to bacterial cell components according to claim 1, wherein the model non-human animal is unresponsive to peptidoglycan as [which is] a bacterial cell component.

5. (twice amended) The model non-human animal being unresponsive to bacterial cell components according to claim 1, wherein the model non-human animal is unresponsive to endotoxin as [which is] a bacterial cell component.

6. (twice amended) The model non-human animal being unresponsive to bacterial cell components according to claim 1, wherein the model non-human animal is unresponsive to lipoteichoic [lopoteichoic] acid as [which is] a bacterial cell component.

7. (twice amended) The model non-human animal being unresponsive to bacterial cell components according to claim 1, wherein the model non-human animal is unresponsive to Mycobacterium tuberculosis lysate as [which is] a bacterial cell component.